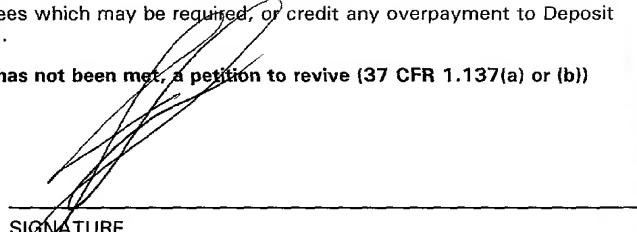


U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE (Rev. 12-29-99)		ATTORNEY'S DOCKET NUMBER 022701-907
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5) 09/719839 Unassigned
INTERNATIONAL APPLICATION NO. PCT/FR99/01442	INTERNATIONAL FILING DATE 16 June 1999	PRIORITY DATE CLAIMED 16 June 1998
TITLE OF INVENTION METHOD FOR PREPARING P-HYDROXYMANDELIC COMPOUNDS OPTIONALLY SUBSTITUTED		
APPLICANT(S) FOR DO/EO/US Isabelle JOUVE; Frederic FOURNET; Jean FRAGNON		
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:		
<p>1. <input checked="" type="checkbox"/> This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.</p> <p>2. <input type="checkbox"/> This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.</p> <p>3. <input checked="" type="checkbox"/> This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and the PCT Articles 22 and 39(1).</p> <p>4. <input checked="" type="checkbox"/> A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.</p> <p>5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2))</p> <ul style="list-style-type: none"> a. <input checked="" type="checkbox"/> is transmitted herewith (required only if not transmitted by the International Bureau). b. <input checked="" type="checkbox"/> has been transmitted by the International Bureau. c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US) <p>6. <input checked="" type="checkbox"/> A translation of the International Application into English (35 U.S.C. 371(c)(2)).</p> <p>7. <input type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))</p> <ul style="list-style-type: none"> a. <input type="checkbox"/> are transmitted herewith (required only if not transmitted by the International Bureau). b. <input type="checkbox"/> have been transmitted by the International Bureau. c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired. d. <input type="checkbox"/> have not been made and will not be made. <p>8. <input type="checkbox"/> A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).</p> <p>9. <input type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).</p> <p>10. <input type="checkbox"/> A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).</p>		
Items 11. to 16. below concern other document(s) or information included:		
<p>11. <input checked="" type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98.</p> <p>12. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.</p> <p>13. <input checked="" type="checkbox"/> A FIRST preliminary amendment.</p> <p><input type="checkbox"/> A SECOND or SUBSEQUENT preliminary amendment.</p> <p>14. <input type="checkbox"/> A substitute specification.</p> <p>15. <input type="checkbox"/> A change of power of attorney and/or address letter.</p> <p>16. <input type="checkbox"/> Other items or information:</p>		

U.S. APPLICATION NO. (If known / see 37 C.F.R. 1.10)		INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
Unassigned 09719839		PCT/FR99/01442	022701-907
17. <input checked="" type="checkbox"/> The following fees are submitted:			CALCULATIONS PTO USE ONLY
Basic National Fee (37 CFR 1.492(a)(1)-(5)):			
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO \$1,000.00 (960)			
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO \$860.00 (970)			
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO \$710.00 (958)			
International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) \$690.00 (956)			
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) \$100.00 (962)			
ENTER APPROPRIATE BASIC FEE AMOUNT =			\$ 860.00
Surcharge of \$130.00 (154) for furnishing the oath or declaration later than months from the earliest claimed priority date (37 CFR 1.492(e)).			20 <input type="checkbox"/> 30 <input type="checkbox"/>
			\$
Claims	Number Filed	Number Extra	Rate
Total Claims	26 -20 =	0	X\$18.00 (966) \$ 0
Independent Claims	1 -3 =	0	X\$80.00 (964) \$ 0
Multiple dependent claim(s) (if applicable)			+\$270.00 (968) \$
TOTAL OF ABOVE CALCULATIONS =			\$ 860.00
Reduction for 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).			\$ -
SUBTOTAL =			\$ 860.00
Processing fee of \$130.00 (156) for furnishing the English translation later than months from the earliest claimed priority date (37 CFR 1.492(f)).			20 <input type="checkbox"/> 30 <input type="checkbox"/>
			\$ +
TOTAL NATIONAL FEE =			\$ 860.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 (581) per property +			\$
TOTAL FEES ENCLOSED =			\$ 860.00
			Amount to be: refunded \$
			charged \$
a. <input checked="" type="checkbox"/> A check in the amount of \$ 860.00 to cover the above fees is enclosed.			
b. <input type="checkbox"/> Please charge my Deposit Account No. 02-4800 in the amount of \$ to cover the above fees. A duplicate copy of this sheet is enclosed.			
c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-4800. A duplicate copy of this sheet is enclosed.			
NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.			
SEND ALL CORRESPONDENCE TO:			
Norman H. Stepno BURNS, DOANE, SWECKER & MATHIS, L.L.P. P.O. Box 1404 Alexandria, Virginia 22313-1404 (703) 836-6620			
 SIGNATURE Teresa Stanek Rea NAME 30,427 REGISTRATION NUMBER			

09/719839
526 Rec'd PCT/PTO 18 DEC 2000

Patent
Attorney's Docket No. 022701-907

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of)
Isabelle JOUVE et al.) Group Art Unit: Unassigned
Application No.: Unassigned) Examiner: Unassigned
(Corresponds to PCT/FR99/01442))
International Filing Date: 16 June 1999)
For: METHOD FOR PREPARING P-)
HYDROXYMANDELIC COMPOUNDS)
OPTIONALLY SUBSTITUTED)

PRELIMINARY AMENDMENT

BOX PCT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to examination, please amend the above-captioned application as follows:

IN THE CLAIMS:

Kindly amend the claims as follows.

Kindly cancel claim 1, without prejudice or disclaimer and insert claim 27, in lieu thereof:

Claim 2, line 1, change "1" to --27-- and change "characterised in that" to

--wherein--;

line 15, delete "preferably a fluorine, chlorine or bromine atom,".

Claim 3, line 1, change "either claim 1 or claim 2" to --claim 27-- and change "characterised in that" to --wherein--;
lines 6-7, delete "and preferably from 1 to 4 carbon atoms,";
lines 8-9, delete "preferably from 1 to 4 carbon atoms,".

Claim 4, line 1, change "one of claims 1 to 3" to --claim 27-- and change "characterised in that" to --wherein--;
line 5, delete "preferably".

Claim 5, line 1, change "one of claims 1 to 4" to --claim 27-- and change "characterised in that" to --wherein--;
line 3, after "guetol," insert --and--.

Claim 6, line 1, change "one of claims 1 to 5" to --claim 27-- and change "characterised in that" to --wherein--.

Claim 7, line 1, change "characterised in that" to --wherein--.

Claim 8, line 1, change "characterised in that" to --wherein--;
line 3, delete "preferably";
line 4, delete ", generally 1 to 3 unsaturations";

lines 15-16, delete "preferably a fluorine, chlorine or bromine atom,".

Claim 9, line 1, change "characterised in that" to --wherein--;
lines 2-3, delete "an aromatic hydrocarbon residue, and, in particular, ";
line 7, delete "preferably from 0 to 3, ".

Claim 10, line 1, change "characterised in that" to --wherein--.

Claim 11, line 1, change "characterised in that" to --wherein--;
lines 3-4, delete ", generally having 3 to 7 carbon atoms, preferably 6 carbon atoms, in the ring".

Claim 12, line 1, change "one of claims 6 to 11" to --claim 6-- and change "characterised in that" to --wherein--.

13. (Amended) A process according to claim 6, [characterised in that] wherein the catalyst is a carrier compound with at least two carboxylic functions corresponding to formula (II) selected from the group consisting of:

[- dicarboxylic aliphatic acids, such as:]

. oxalic acid

- . malonic acid
 - . succinic acid
 - . glutaric acid
 - . adipic acid
 - . 2,4-dimethyl adipic acid
 - . pimelic acid
 - . suberic acid
 - . azelaic acid
 - . sebacic acid
 - . dodecane dioic acid
 - . fumaric acid
 - . maleic acid
- [- cycloalkanedicarboxylic acids, such as]
- . cyclohexane 1,4-dicarboxylic acid,
- [- aromatic dicarboxylic acids, such as:]
- . phthalic acid
 - . isophthalic acid
 - . terephthalic acid
 - . phenylenediacetic acid
 - . naphthalene 1,5-dicarboxylic acid
 - . naphthalene 1,6-dicarboxylic acid
 - . 4,4'-diphenylcarboxylic acid

- . 3,3'-diphenylcarboxylic acid
- . bis(4-hydroxycarbonyl) phenyl oxide
- . bis(3-hydroxycarbonyl) phenyl oxide
- . 4,4'-dihydroxycarbonyl diphenylsulphone
- . 3,3'-dihydroxycarbonyl diphenylsulphone
- [-] . pyrimidine or imidazole dicarboxylic acids.
- [-] aminopolycarboxylic acids:]
 - . ethylenediaminetetraacetic acid (E.D.T.A.)
 - . diethylenetriaminopentacetic acid (D.T.P.A.)
 - . nitrilotriacetic acid (N.T.A.) and
 - . N-(2-hydroxyethyl)ethylene diaminotriacetic acid (H.E.D.T.A.).

Claim 14, line 1, change "one of claims 1 to 13" to --claim 27-- and change "characterised in that" to --wherein--;
line 2, delete ", in particular from 0.1 to 3% acetic acid".

Claim 15, line 1, change "one of claims 1 to 14" to --claim 27-- and change "characterised in that" to --wherein--;
lines 2-3, delete ", preferably in the region of 50% by weight".

Claim 16, line 1, change "one of claims 1 to 15" to --claim 27-- and change "characterised in that" to --wherein--;

line 3, delete "and is preferably selected between 2.0 and 3.0".

Claim 17, line 1, change "one of claims 1 to 16" to --claim 27-- and change "characterised in that" to --wherein--.

Claim 18, line 1, change "one of claims 1 to 17" to --claim 27-- and change "characterised in that" to --wherein--;

line 2, delete "preferably comprised";

line 3, delete ", and more particularly in the region of 1 mole/litre".

Claim 19, line 1, change "one of claims 1 to 18" to --claim 27-- and change "characterised in that" to --wherein--;

line 3, delete ", and preferably between 0.01 and 0.02".

Claim 20, line 1, change "one of claims 1 to 19" to --claim 27-- and change "characterised in that" to --wherein--;

lines 3-4, delete ", preferably between 1 and 2%".

Claim 21, line 1, change "one of claims 1 to 20" to --claim 27-- and change "characterised in that" to --wherein--.

Claim 22, line 1, change "characterised in that" to --wherein--;

line 2, delete "preferably between 1.2 and 2.6%,".

Claim 23, line 1, change "one of claims 1 to 22" to --claim 27-- and change "characterised in that" to --wherein--.

Claim 24, line 1, change "one of claims 1 to 23" to --claim 27-- and change "characterised in that" to --wherein--;
line 2, delete ", preferably between 30°C and 40°C".

25. (Amended) [Use of the optionally substituted p-hydroxymandelic compounds obtained according to one of claims 1 to 24 as intermediates] An intermediate for the production of hydroxyarylacetic acids, hydroxyarylglyoxylic acids, or hydroxyaromatic aldehydes comprising using the optionally substituted p-hydroxymandelic compounds obtained according to the process of claim 27.

26. (Amended) [Use of p-hydroxymandelic acid and 3-methoxy p-hydroxymandelic, 3-ethoxy p-hydroxymandelic acids or 3-isopropoxy p-hydroxymandelic acids obtained in accordance with the preparation process described in one of claims 1 to 24] A process for the production of 4-hydroxy benzaldehyde and vanillin and analogues by oxidation of said acids using p-hydroxymandelic acid and 3-methoxy p-hydroxymandelic acid, 3-ethoxy p-hydroxymandelic acid, or 3-isopropoxy p-hydroxymandelic acid obtained in accordance with claim 27.

--27. A process for the preparation of an optionally substituted p-hydroxymandelic compound, comprising condensing, in water and in the presence of an alkaline agent, (1) a hydroxylated aromatic compound with (2) glyoxylic acid, the para-position of said hydroxylated aromatic compound being free and said condensation being carried out in the presence of a catalytically effective amount of (3) a polycarboxylic compound.--

REMARKS

Entry of the foregoing amendment(s) is respectfully requested.

The claims have been amended to eliminate multiple dependency and to place them in better condition for U.S. patent practice.

Should the Examiner have any questions concerning the subject application, a telephone call to the undersigned would be appreciated.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By:

Teresa Stanek Rea
Registration No. 30,427

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Date: December 18, 2000

WO 99/65853

PCT/FR99/01442

A PROCESS FOR THE PREPARATION
OF OPTIONALLY SUBSTITUTED P-HYDROXYMANDELIC COMPOUNDS

A subject of the present invention is a process for the preparation of optionally substituted p-hydroxymandelic compounds and derivatives.

In the disclosure of the invention which follows, the term, "optionally substituted p-hydroxymandelic compounds" is used to refer to an aromatic compound which carries at least one -CHOH-COOH group in para position of a hydroxyl group.

The present invention relates, more particularly, to the preparation of p-hydroxymandelic acid and 3-methoxy p-hydroxymandelic acid.

One of the conventional synthesis routes for p-hydroxymandelic acids consists in carrying out the condensation, in alkaline medium, of glyoxylic acid on phenol and/or its corresponding derivatives.

The yield is limited by the fact that the condensation reaction is not selective and also produces o-hydroxymandelic acids and dimandelic acids.

Furthermore, the reaction yield is reduced due to a parasitic secondary reaction. In fact, glyoxylic acid in aqueous alkaline medium is converted according to Cannizaro's reaction into oxalic and glycolic acids.

In order to prevent this Cannizaro's reaction from becoming dominant and destroying the glyoxylic acid, a proposal has been made in FR-A 2 132 364 for the condensation reaction to be carried out in a dilute aqueous medium and at low temperature or ambient temperature.

In view of the difficulty in obtaining satisfactory reaction yields, it is important to control the various parameters of the process, and, in particular, the quality of the glyoxylic acid used.

The most worthwhile process from an industrial viewpoint for the preparation of glyoxylic acid consists in oxidising the glyoxal with nitric acid. In this way, aqueous solutions of glyoxylic acid are obtained, which, in addition to unreacted glyoxal, also contain oxalic acid, organic acids, such as formic acid, acetic acid, glycolic acid, and nitric acid.

Until now, new methods have been constantly sought for the separation and purification of glyoxylic acid.

Therefore, a process was proposed in DE-A 1 198 339 which first and foremostly permitted the nitric acid to be eliminated, followed by the oxalic acid using basic ion exchange resins, followed by the glyoxal and the other impurities by over-concentration of the solution and crystallisation.

In DE-A 2 501 743, a process was disclosed in which the glyoxylic acid is separated from these impurities by extraction using aliphatic or cycloaliphatic alcohols, or aliphatic esters of alcohols with low carbon condensation.

A process for obtaining aqueous solutions of glyoxylic acid free from other acids has also been described in FR-A 2 552 426 which consists in treating the starting solution with an organic nitrogenous compound, preferably a tertiary amine, at a temperature which is at the most equal to 50°C, then in extracting the glyoxylic acid by extraction of the organic phase with water, at a higher temperature.

A constant concern has therefore been noted in the prior art of providing a solution of glyoxylic acid which is free of impurities.

Running counter to this teaching, it has been found that within the scope of preparing optionally substituted p-hydroxymandelic compounds condensation of glyoxylic acid and of the corresponding phenol is carried out with an increased yield, provided that said reaction is carried out in the presence of a dicarboxylic acid used in a certain quantity.

A precise subject of the present invention is a process for the preparation of optionally substituted p-hydroxymandelic compounds and derivatives, which consists in carrying out the condensation, in water, in the presence of an alkaline agent, of an aromatic carrier compound

with at least one hydroxyl group and the para position of which is free, with glyoxylic acid, said process being characterised in that the reaction is carried out in the presence of an effective quantity of a carrier compound with at least two carboxylic functions.

In accordance with the process of the invention, the use of a catalyst according to the invention allows the reaction yield to be increased.

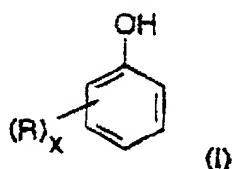
Another advantage of the process according to the invention is that it can involve a more technical glyoxylic acid containing, inter alia, oxalic acid.

The process according to the invention is used, most particularly, with phenol but also with substituted phenols which have at least one non-substituted para position.

The aromatic nucleus carries at least one hydroxyl group, but it can also carry one or more other substituents. Generally, "several substituents" means less than four substituents per aromatic nucleus.

Any substituent can be present provided that it is does not interfere in the reaction of the invention.

Therefore, the process according to the invention is well suited for use with hydroxylated aromatic compounds corresponding to the following formula (I):



in which formula (I):

- the para position is free,
- x is an integer between 1 and 4,
- R represents :
 - a hydrogen atom,

- a hydrocarbon group having from 1 to 20 carbon atoms selected from the alkyl, alkoxy, hydroxyalkyl, cycloalkyl, aryl, phenoxy, alkoxyalkyl, fluoroalkyl, hydroxyalkoxyalkylene groups,
- a hydroxyl group,
- a -CHO group,
- an acyl group having from 2 to 6 carbon atoms,
- a halogen atom, preferably a fluorine, chlorine or bromine atom,
- two R groups placed on two vicinal carbon atoms can form together and with the carbon atoms which carry them a benzene ring.

Examples of R radicals which are capable of being carried by the aromatic nucleus are given hereinafter:

- alkyl radicals, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, n-octyl, 2-ethyl hexyl, decyl, octadecyl, eicosyl,
- alkoxy radicals, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, hexyloxy, decyloxy, hexadecyloxy, octadecyloxy, or a phenoxy radical,
- hydroxyalkyl radicals, such as hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxyhexyl, hydroxydecyl,
- cycloalkyl radicals, such as cyclopentyl, cyclohexyl, cycloheptyl,
- fluoroalkyl radicals, such as fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl, 1,1,1-trifluoro ethyl, pentafluoroethyl, fluoropropyl, fluorobutyl, trifluoroamyl,
- hydroxyalkyoxyalkylene radicals, such as hydroxymethyloxyethylene, hydroxyethyl di-(oxyethylene), hydroxyethyl tri-(oxyethylene), 1,2-hydroxyethyloxypropylene, hydroxyethyloxybutylene, hydroxypropyloxypropylene, hydroxybutyloxybutylene, hydroxybutyl di-(oxybutylene),
- halogen atoms, such as fluorine, chlorine, bromine, or iodine.

Quite preferably, hydroxylated aromatic compounds are used in the process of the invention, corresponding to the general formula (I), in which:

- x is equal to 0, 1, 2 or 3,
- R represents one of the following groups or functions:
 - . a hydrogen atom,

- . a linear or branched alkyl radical having from 1 to 10 carbon atoms, and preferably from 1 to 4 carbon atoms,
- . a linear or branched alkoxy radical having from 1 to 10 carbon atoms, preferably from 1 to 4 carbon atoms,
- . an -OH group,
- . a -CHO group,
- . a halogen atom,
- . a -CF₃ group.

Still more preferably, the compounds of formula (I) are selected in which the R radicals which are identical or different are a hydrogen atom, a linear or branched alkyl radical with 1 to 4 carbon atoms, such as the methyl, ethyl, n-propyl, isopropyl, n-butyl or isobutyl radicals, a linear or branched alkoxy radical having 1 to 4 carbon atoms, such as the methoxy or ethoxy radicals, a -CHO group, or a chlorine atom, and x is preferably equal to 0 or 1.

By way of illustration of compounds corresponding to formula (I), the following can be mentioned:

- those corresponding to formula (I) in which x is equal to 0, such as phenol,
- those corresponding to formula (I) in which x is equal to 1, such as
 - . pyrocatechin
 - . resorcin
 - . o-cresol
 - . m-cresol
 - . 2-ethyl phenol
 - . 3-ethyl phenol
 - . 2-propyl phenol
 - . 2-sec-butyl phenol
 - . 2-tert-butyl phenol
 - . 3-tert-butyl phenol
 - . 2-methoxy phenol (guaiacol)
 - . 3-methoxy-phenol
 - . 2-ethoxy phenol (guetol)
 - . 2-isopropoxy phenol
 - . salicylic aldehyde

- . methyl salicylate
- . 2-chloro phenol
- . 3-chloro phenol
- . 3-nitro phenol
- those corresponding to formula (I) in which x is equal to 2, such as:
 - . 2,3-dimethyl phenol
 - . 2,5-dimethyl phenol
 - . 3,5-dimethyl phenol
 - . 2-hydroxy 5-acetamido benzaldehyde
 - . 2-hydroxy 5-ethamido benzaldehyde
 - . 2,3-dichloro phenol
 - . 2,5-dichloro phenol
 - . 3,5-dichloro phenol
 - . pyrogallol
- those corresponding to formula (I) in which x is equal to 3, such as:
 - . 2,3,5-trimethyl phenol
 - . 3,5-di-tert butyl phenol
 - . 2,3,5-trichloro phenol
- those corresponding to formula (I) having a naphthalenic radical, such as:
 - . 1-naphthol
 - . 2-naphthol
 - . 1,2-dihydroxy naphthalene
 - . 1,5-dihydroxy naphthalene
 - . 2,3-dihydroxy naphthalene
 - . 2,6-dihydroxy naphthalene
 - . 2,7-dihydroxy naphthalene
 - . 6-bromo 2-naphthol
- those corresponding to formula (I) having a chain formation of benzene nuclei:
 - . 2-phenoxy phenol
 - . 3-phenoxy phenol

Of the list of afore-mentioned compounds, the aromatic carrier compounds preferably used which have at least one hydroxyl group are: phenol, o-cresol, m-cresol, 3-ethyl phenol, 2-tert-butyl phenol, guaiacol, guetol.

As regards the type of catalyst used, an at least difunctional acid can be used which corresponds to the following formula (II):



in which formula (II), R_1 represents a valency bond or an optionally substituted hydrocarbon radical containing 1 to 40 carbon atoms.

To be more exact, in formula (II), R_1 symbolises a substituted or non-substituted hydrocarbon radical which can be a linear or branched, saturated or unsaturated acyclic aliphatic radical; a monocyclic or polycyclic, saturated, unsaturated, or aromatic carbocyclic radical; a monocyclic or polycyclic, saturated, unsaturated or aromatic heterocyclic radical.

The carrier compounds with at least two carboxylic functions of general formula (II) in which R_1 represents a valency bond or a divalent radical preferably having 1 to 15 carbon atoms are quite particularly suitable for implementation of the process according to the invention.

The carrier compounds with at least two carboxylic functions of general formula (II) in which R_1 represents a linear or branched, saturated or unsaturated aliphatic residue are particularly well suited for use of the process according to the invention.

To be more exact, R_1 represents a linear or branched, acyclic aliphatic residue having preferably 1 to 12 carbon atoms, saturated or containing one or more unsaturations on the chain, generally 1 to 3 unsaturations which can be single or conjugated double bonds, or triple bonds.

The hydrocarbon chain can optionally be:

- (1) - interrupted by one of the following groups called Y:

$$\begin{array}{c} -\text{O}- ; -\text{CO}- ; -\text{COO}- ; -\underset{\text{R}_2}{\text{N}}- ; -\underset{\text{R}_2}{\text{CO}}-\underset{\text{R}_2}{\text{N}}- ; -\text{S}- ; -\text{SO}_2- \end{array}$$

in which formula R_2 represents hydrogen or a linear or branched alkyl radical having 1 to 4 carbon atoms, preferably a methyl or ethyl radical, or a radical of $-(\text{CH}_2)_p-\text{COOH}$ type in which p is a number between 1 and 5,

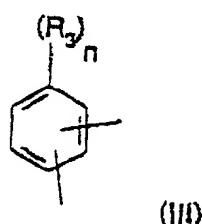
(2) - and/or bearing one of the following substituents:

- OH; - COOH ; - CHO ; - NO₂ ; - CN ; - NH₂ ; - SH ; - X ; CF₃
- NH - [(CH₂)_p - COOH] or - N -[(CH₂)_p - COOH]₂

with X representing a halogen atom, preferably a fluorine, chlorine or bromine atom, and p having the meaning given hereinabove.

The carrier compounds with at least two carboxylic functions of general formula (II) in which R₁ represents a monocyclic or polycyclic hydrocarbon residue are also suitable for implementation of the process according to the invention.

R₁ preferably represents an aromatic hydrocarbon residue, and, in particular, a benzene residue corresponding to the general formula (III):



in which formula (III):

- n is an integer from 0 to 4, preferably from 0 to 3,
- R₃ represents one of the following groups or functions,
 - . a hydrogen atom,
 - . a linear or branched alkyl radical having from 1 to 4 carbon atoms,
 - . a linear or branched alkoxy radical having from 1 to 4 carbon atoms,
 - . a methylene or ethylene dioxy radical,
 - . a -CHO group,
 - . a phenyl or benzyl radical,
 - . a halogen atom,

Even more preferably, the compounds of formula (II) are selected in which the R₁ radical corresponds to formula (III) in which the R₃ radicals, which are identical or different, are a hydrogen atom, a methyl radical, a methoxy radical, a -CHO group.

The carrier compounds having at least two carboxylic functions can correspond to general formula (II) in which the R₁ radical represents a polycyclic aromatic hydrocarbon divalent residue; the rings can form between themselves ortho condensed, ortho- and peri-condensed

systems. More particularly, a naphthylenic residue can be mentioned; said rings being able to be substituted by 1 to 4 R₃ radicals, preferably by 1 to 3, R₃ having the meanings stated hereinabove for the substituents of the aromatic hydrocarbon residue of general formula (III).

In general formula (II) of the carrier compounds with at least two carboxylic functions, R₁ can also represent a carbocyclic residue which is saturated or which comprises 1 or 2 unsaturations in the ring, generally having from 3 to 7 carbon atoms, preferably 6 carbon atoms in the ring; said ring being able to be substituted by 1 to 5, preferably 1 to 3, R₃ radicals, R₃ having the meanings stated hereinabove for the substituents of the aromatic hydrocarbon residue of general formula (III).

As preferred examples of R₁ radicals the cyclohexane-diyl radicals can be mentioned which are optionally substituted by linear or branched alkyl radicals having 1 to 4 carbon atoms.

The carrier compounds with at least two carboxylic functions can also correspond to formula (II) in which R₁ represents a divalent radical constituted by a chain formation of two to four residues as defined hereinabove, an aliphatic residue, an aromatic residue, or a cycloaliphatic residue. These can be connected together by a valency bond or by a function group which can be, in particular, a group selected from the groups called Y.

Some examples of R₁ radicals are given hereinafter:

- CH₂-C₆H₄-;
- CH₂-CH₂-C₆H₄-;
- CH₂-O-C₆H₄-;
- CH₂-O-C₆H₄-;
- CH₂-O-C₆H₄-CH₂-;
- C₆H₄-C₆H₄-;
- C₆H₄-CH₂-C₆H₄-;
- C₆H₄-O-C₆H₄-;
- CH₂-C₆H₄-CH₂-C₆H₄-CH₂-

The following carrier compounds with at least two carboxylic functions can be mentioned, quite particularly, by way of catalysts which are suitable for the present invention:

- dicarboxylic aliphatic acids, such as:
 - . oxalic acid
 - . malonic acid
 - . succinic acid
 - . glutaric acid
 - . adipic acid
 - . 2,4-dimethyl adipic acid
 - . pimelic acid
 - . suberic acid
 - . azelaic acid
 - . sebacic acid
 - . dodecane dioic acid
 - . fumaric acid
 - . maleic acid
- cycloalkanedicarboxylic acids, such as cyclohexane 1,4-dicarboxylic acid,
- aromatic dicarboxylic acids, such as:
 - . phthalic acid
 - . isophthalic acid
 - . terephthalic acid
 - . phenylenediacetic acid
 - . naphthalene 1,5-dicarboxylic acid
 - . naphthalene 1,6-dicarboxylic acid
 - . 4,4'-diphenylcarboxylic acid
 - . 3,3'-diphenylcarboxylic acid
 - . bis(4-hydroxycarbonyl) phenyl oxide
 - . bis(3-hydroxycarbonyl) phenyl oxide
 - . 4,4'-dihydroxycarbonyl diphenylsulphone
 - . 3,3'-dihydroxycarbonyl diphenylsulphone
- pyrimidine or imidazole dicarboxylic acids.

In the afore-mentioned list of dicarboxylic acids, the compounds preferably used are: oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, sebacic acid, phthalic acid, isophthalic acid, terephthalic acid.

Aminopolycarboxylic acids are also perfectly well suited for implementation of the process according to the invention. As examples of aminopolycarboxylic acids suitable for use in the process of the invention mention can be made of the following, inter alia:

- . ethylenediaminetetracetic acid (E.D.T.A.)
- . diethylenetriaminopentacetic acid (D.T.P.A.)
- . nitrilotriacetic acid (N.T.A.)
- . N-(2-hydroxyethyl)ethylene diaminetriacetic acid (H.E.D.T.A.)

Of the afore-mentioned aminopolycarboxylic acids, ethylenediaminetetracetic acid is preferably selected.

According to the process of the invention, the reaction is carried out in the presence of an alkali metal hydroxide which can be sodium or potassium hydroxide.

For economic considerations, sodium hydroxide is preferably selected.

With regard to the concentrations and quantities of reagents to be used, the preferred conditions are defined hereinbelow.

In accordance with the process according to the invention a solution of glyoxylic acid is used. The concentration of said solution is not critical and can vary greatly, e.g. between 15 and 70% by weight. Preferably, commercial solutions are used, the concentration of which is approximately 50%.

According to the process of the invention, the glyoxylic acid is reacted on the excess of the hydroxylated aromatic compound of formula (I). The molar ratio between the hydroxylated aromatic compound of formula (I) and the glyoxylic acid varies between 1.5 and 4.0 and is preferably selected between 2.0 and 3.0.

The alkali metal hydroxide solution used has a concentration which is generally between 10 and 50% by weight. The concentration of the starting solution is not critical. However, as the concentration of the hydroxylated aromatic compound of formula (I) is advantageously low in the reaction medium, a dilute solution of alkali metal is used to carry out the dilution of the reaction medium.

The quantity of alkali metal hydroxide introduced into the reaction medium takes account of the quantity necessary to saponify the hydroxyl function of the hydroxylated aromatic compound of formula (I) and of the quantity necessary to saponify the carboxylic function of the glyoxylic acid.

If the hydroxylated aromatic compound of formula (I) has saponifiable functions other than the hydroxyl group, the quantity of alkali metal hydroxide necessary to saponify all the saponifiable functions which can be hydroxyl groups and/or COOH carboxylic functions is therefore introduced.

Generally, the quantity of alkali metal hydroxide can vary greatly and be equal to, or approximately equal to, the stoichiometry, or in excess. Generally, the quantity of alkali metal hydroxide varies between 80 and 120% of the stoichiometric quantity.

The concentration of the hydroxylated aromatic compound of formula (I) is preferably between 0.5 and 1.5 moles/litre, and, more particularly, in the region of 1 mole/litre.

With regard to the quantity of catalyst used, this is determined in such a way that the molar ratio between the catalyst and the hydroxylated aromatic compound of formula (I) is between 0.005 and 0.025, and preferably between 0.01 and 0.02.

The quantity of catalyst used, as expressed by the ratio between the number of moles of catalyst and the number of moles of glyoxylic acid is advantageously selected to be between 0.5 and 2.5%, preferably between 1 and 2%.

The preferred catalyst is oxalic acid.

The commercial solutions of glyoxalic acid can contain very low quantities of oxalic acid. The oxalic acid of the reaction can therefore be provided, in part, by the starting solution. In this case, it will be necessary to complete the quantity of oxalic acid by the addition of oxalic acid or of any other dicarboxylic acid in order that the afore-mentioned ratios are observed.

According to a preferred embodiment of the invention, a solution of glyoxylic acid is advantageously used containing between 0.6 and 3%, preferably between 1.2 and 2.6%, by weight of oxalic acid, expressed in relation to the weight of glyoxylic acid.

The reaction temperature is advantageously selected between 20°C and 60°C, and preferably between 30°C and 40°C.

The process according to the invention is carried out at atmospheric pressure, but under a controlled inert gas atmosphere, preferably nitrogen or rare gases, in particular nitrogen.

A preferred practical embodiment of the invention will be given hereinafter.

The solution of glyoxylic acid and catalyst, and, in parallel, the solution of alkali metal hydroxide employed in a quantity necessary to salify the COOH function are introduced into a reaction medium containing the hydroxylated aromatic compound of formula (I), water and the alkali metal hydroxide in a quantity necessary to salify the hydroxyl group and other possible salifiable functions of the compound of formula (I).

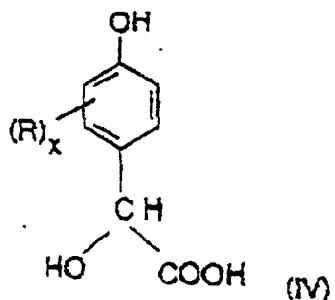
The reaction medium is kept under agitation and at the temperature selected within the afore-mentioned range for a variable period ranging from 1 to 10 hours.

Another variant of the execution of the invention consists in adding the reaction catalyst not to the aqueous solution of glyoxylic acid but simultaneously with the hydroxylated aromatic compound of formula (I).

At the end of the reaction, the optionally substituted p-hydroxymandelic acid obtained is separated in salified form using conventional separation techniques, in particular crystallisation.

The process according to the invention is quite particularly well suited when an aqueous solution of glyoxylic acid is used containing monofunctional acids, such as formic and glycolic acid, and, in particular, when acetic acid is present in a concentration which is variable between 0.1 and 3%.

The process according to the invention results in the production of optionally substituted p-hydroxymandelic compounds which can be represented by the following formula (IV):



in which formula (IV) R and x have the meaning given in formula (I).

These products are particularly worthwhile since they are intermediate products, which, inter alia, allow hydroxyarylacetic acids to be obtained by reduction and hydroxyarylglyoxylic (= hydroxyaryl α -oxo acetic) acids or hydroxyaromatic aldehydes to be obtained by oxidation.

A preferred use of the invention is the preparation of hydroxyaromatic aldehydes by oxidation of the compounds of formula (IV) obtained according to the invention.

The oxidation of the compounds of formula (IV) can be carried out according to the techniques described in writings. Thus, reference can be made to P. HEBERT [Bull. Soc. Chim. France, 27, p. 45-55 (1920)] and to NAGAI SHIGEKI et al [JP-A 76/128934]. The oxidation is generally carried out using oxygen or air under pressure, in the presence of an appropriate catalyst, such as derivatives of chromium, cobalt, copper, vanadium or osmium, for example.

Therefore, the invention allows easy access to 4-hydroxy benzaldehyde and to vanillin and its analogues, e.g. 3-ethyl, 3-isopropyl vanillin, by oxidation respectively of p-hydroxymandelic acid and of 3-methoxy p-hydroxymandelic acids, and 3-ethoxy p-hydroxy-mandelic or 3-isopropoxy p-hydroxymandelic acids.

The following examples illustrate the invention, without however limiting it.

In the examples, the percentages stated are expressed by weight.

The abbreviations mentioned in the examples have the following meanings:

Conversion (TT) = $\frac{\text{number of moles of guaiacol converted}}{\text{number of moles of guaiacol introduced}}$

Yield (RR) = $\frac{\text{number of moles of mandelic acid formed}}{\text{number of moles of mandelic acid introduced}}$

Selectivity (RT) = $\frac{\text{number of moles of mandelic acid formed}}{\text{number of moles of guaiacol converted}}$

Example 1

- 600 g distilled water,
- 91.6 g (0.687 mol) of a 30% aqueous soda solution,
- 93 g (0.750 mol) guaiacol

are introduced into a 1-litre glass reaction vessel equipped with a double jacket, a pH electrode, a temperature probe, a condenser, an inert gas supply, and a mechanical agitation device.

An inert atmosphere is established, and the reaction mixture is brought to 35°C, and 50.7 g (0.380 mol) of a 30% by weight aqueous soda solution and 55.2 g of a 50% by weight aqueous glyoxylic acid solution are added simultaneously over a period of 2 hours. Oxalic acid is added with the glyoxylic acid introduced in such a quantity that it represents 0.75% by weight of the glyoxylic acid solution.

The glyoxylic acid solution introduced contains 0.3% oxalic acid, 0.9% lower carboxylic acids such as acetic acid, and formic acid and glycolic acid in a respective quantity of less than 0.1%.

The reaction mixture is maintained at 35°C for 2 hours.

At the end of the reaction, the reaction products are analysed using high performance liquid chromatography.

The results obtained were as follows:

- conversion:
 - . TT = 47.3%
- 4-hydroxy 3-methoxy mandelic acid:
 - . RR = 79.7%
 - . RT = 84.2%
- 2-hydroxy 3-methoxy mandelic acid:
 - . RR = 4.8%
 - . RT = 5.1%
- 2-hydroxy 3-methoxy 1.5-dimandelic acid:
 - . RR = 8.0%
 - . RT = 4.0%

Comparative Example 2

Example 1 is reproduced, except that no oxalic acid is introduced.

The results obtained were as follows:

- conversion:
 - . TT = 46.1%
- 4-hydroxy 3-methoxy mandelic acid:
 - . RR = 76.9%
 - . RT = 83.0%
- 2-hydroxy 3-methoxy mandelic acid:
 - . RR = 5.1%
 - . RT = 5.5%
- 2-hydroxy 3-methoxy 1.5-dimandelic acid:
 - . RR = 7.5%
 - . RT = 4.1%

Example 3

In this example, Example 1 is reproduced except that a 50% solution of glyoxylic acid is used containing 0.4% by weight of oxalic acid.

The results obtained are as follows:

- conversion:

$$\text{. TT} = 48\%$$

- 4-hydroxy 3-methoxy mandelic acid:

$$\text{. RR} = 79.3\%$$

$$\text{. RT} = 83.1\%$$

- 2-hydroxy 3-methoxy mandelic acid:

$$\text{. RR} = 5.6\%$$

$$\text{. RT} = 5.8\%$$

- 2-hydroxy 3-methoxy 1,5-dimandelic acid:

$$\text{. RR} = 8.0\%$$

$$\text{. RT} = 4.2\%$$

Examples 4 to 8

In the following set of examples Example 1 is reproduced except that different types of dicarboxylic acids are used, such as malonic acid, succinic acid and E.D.T.A.

The glyoxylic acid solution used contains oxalic acid at a rate of 0.09%, lower carboxylic acids such as acetic acid at a rate of 1%, formic acid and glycolic acid at respective quantities of less than 0.3%.

All the conditions of the examples and the results obtained are indicated in Table I.

Table 1

Ref. ex.	Dicarboxylic acid (%)	TT	RR			RT		
			para	ortho	di	para	ortho	di
4	-	45.2	77.5	4.9	7.6	84.3	5.3	4.1
5	oxalic acid (2.0%)	47.8	80.1	4.8	8.1	83.0	5.0	4.2
6	malonic acid (2.0%)	46.1	80.2	5.2	7.6	84.8	5.5	4.1
7	succinic acid (1.9%)	48.0	81.4	5.6	8.0	85.0	5.8	4.2
8	E.D.T.A. (1.5%)	44.5	80.6	4.9	7.7	88.0	5.4	4.2

* = dicarboxylic acid expressed in molar percent in relation to the glyoxylic acid.

Examples 9 to 11

In the following examples, the quantity of oxalic acid used in the glyoxylic acid solution is increased.

The procedure of Example 1 is followed, and a 50% glyoxylic acid solution is used, the composition of which is given in Examples 4 to 8.

The results obtained are indicated in the following table:

Table II

Ref. ex.	Oxalic acid *	TT	RR			RT		
			para	ortho	di	para	ortho	di
9	1.00	45.2	79.5	5.1	7.6	86.7	5.6	4.1
10	1.9	47.8	80.1	4.8	8.1	83.0	5.0	4.2
11	1.78	46.1	76.5	4.8	8.0	83.0	5.2	4.3

* = concentration of oxalic acid in % by weight in the glyoxylic acid solution.

In said table, the abbreviations, "ortho", "para" and "di" mean :

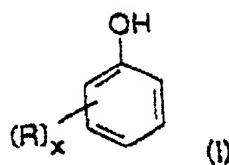
- 4-hydroxy 3-methoxy mandelic acid = para

- 2-hydroxy 3-methoxy mandelic acid = ortho
- 2-hydroxy 3-methoxy 1,5 dimandelic acid = di

CLAIMS

1 - A process for the preparation of optionally substituted p-hydroxymandelic compounds and derivatives, which consists in carrying out the condensation, in water, in the presence of an alkaline agent, of an aromatic carrier compound with at least one hydroxyl group and the para position of which is free, with glyoxylic acid, said process being characterised in that the reaction is carried out in the presence of an effective quantity of a carrier compound with at least two carboxylic functions.

2 - A process according to claim 1, characterised in that the hydroxylated compound corresponds to the following formula (I):



in which formula (I):

- the para position is free,
- x is an integer between 1 and 4,
- R represents :
 - a hydrogen atom,
 - a hydrocarbon group having from 1 to 20 carbon atoms selected from the alkyl, alkoxy, hydroxyalkyl, cycloalkyl, aryl, phenoxy, alkoxyalkyl, fluoroalkyl, hydroxyalkoxyalkylene groups,
 - a hydroxyl group,
 - a -CHO group,
 - an acyl group having from 2 to 6 carbon atoms,
 - a halogen atom, preferably a fluorine, chlorine or bromine atom,
 - two R groups placed on two vicinal carbon atoms can form together and with the carbon atoms which carry them a benzene ring.

3 - A process according to either claim 1 or claim 2, characterised in that the hydroxylated aromatic compound corresponds to formula (I), in which:

- x is equal to 0, 1, 2 or 3,

- R represents one of the following groups or functions:
 - . a hydrogen atom,
 - . a linear or branched alkyl radical having from 1 to 10 carbon atoms, and preferably from 1 to 4 carbon atoms,
 - . a linear or branched alkoxy radical having from 1 to 10 carbon atoms, preferably from 1 to 4 carbon atoms,
 - . an -OH group,
 - . a -CHO group,
 - . a halogen atom,
 - . a -CF₃ group.

4 - A process according to one of claims 1 to 3, characterised in that the hydroxylated aromatic compound corresponds to formula (I) in which the R radicals which are identical or different are a hydrogen atom, a linear or branched alkyl radical with 1 to 4 carbon atoms, a linear or branched alkoxy radical with 1 to 4 carbon atoms, a -CHO group, a chlorine atom, and x is preferably equal to 0 or 1.

5 - A process according to one of claims 1 to 4, characterised in that the hydroxylated aromatic compound of formula (I) is phenol, o-cresol, m-cresol, 3-ethyl phenol, 2-tert-butyl phenol, guaiacol, guetol, 2-isopropoxy phenol.

6 - A process according to one of claims 1 to 5, characterised in that the catalyst is a compound carrying at least two carboxylic functions corresponding to the following formula (II):



in which formula (II), R₁ represents a valency bond or an optionally substituted hydrocarbon radical containing 1 to 40 carbon atoms.

7 - A process according to claim 6, characterised in that the catalyst is a carrier compound having at least two carboxylic functions corresponding to formula (II) wherein R₁ symbolises a substituted or non-substituted hydrocarbon radical which can be a linear or branched, saturated or unsaturated acyclic aliphatic radical; a monocyclic or polycyclic,

saturated, unsaturated, or aromatic carbocyclic radical; a monocyclic or polycyclic, saturated, unsaturated or aromatic heterocyclic radical.

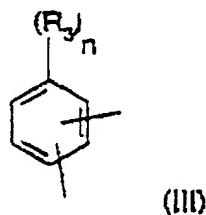
8 - A process according to claim 6, characterised in that the catalyst is a carrier compound with at least two carboxylic functions corresponding to formula (II), in which R₁ represents a linear or branched, acyclic aliphatic residue having preferably 1 to 12 carbon atoms, saturated or containing one or more unsaturations on the chain, generally 1 to 3 unsaturations which can be single or conjugated double bonds, or triple bonds; the hydrocarbon chain can optionally be:

in which formulae R₂ represents hydrogen or a linear or branched alkyl radical having 1 to 4 carbon atoms, or a radical of -(CH₂)_p-COOH type in which p is a number between 1 and 5,

- (2) - and/or bearing one of the following substituents:
- OH; - COOH ; - CHO ; - NO₂ ; - CN ; - NH₂ ; - SH ; - X ; CF₃
- NH - [(CH₂)_P - COOH] or - N - [(CH₂)_P - COOH]₂

with X representing a halogen atom, preferably a fluorine, chlorine or bromine atom, and p having the meaning given hereinabove.

9 – A process according to claim 6, characterised in that the catalyst is a carrier compound with at least two carboxylic functions corresponding to formula (II), in which R₁ represents an aromatic hydrocarbon residue, and, in particular, a benzene residue corresponding to the general formula (III):



in which formula (III):

- n is an integer from 0 to 4, preferably from 0 to 3,
 - R_3 represents one of the following groups or functions.

- . a hydrogen atom,
- . a linear or branched alkyl radical having from 1 to 4 carbon atoms,
- . a linear or branched alkoxy radical having from 1 to 4 carbon atoms,
- . a methylene or ethylene dioxy radical,
- . a -CHO group,
- . a phenyl or benzyl radical,
- . a halogen atom.

10 - A process according to claim 6, characterised in that the catalyst is a carrier compound with at least two carboxylic functions corresponding to formula (II) in which the R₁ radical represents a polycyclic aromatic hydrocarbon divalent residue; the rings can form between themselves ortho-condensed, ortho- and peri-condensed systems.

11 - A process according to claim 6, characterised in that the catalyst is a carrier compound with at least two carboxylic functions corresponding to formula (II), in which R₁ represents a carbocyclic residue which is saturated or contains 1 or 2 unsaturations in the ring, generally having 3 to 7 carbon atoms, preferably 6 carbon atoms, in the ring.

12 - A process according to one of claims 6 to 11, characterised in that the catalyst is a carrier compound with at least two carboxylic functions corresponding to formula (II), in which R₁ represents a divalent radical constituted by a chain formation of two to four residues as defined hereinabove, an aliphatic residue, an aromatic residue or a cycloaliphatic residue, connected together by a valency bond or by a function group.

13 - A process according to claim 6, characterised in that the catalyst is a carrier compound with at least two carboxylic functions corresponding to formula (II) selected from:

- dicarboxylic aliphatic acids, such as:
 - . oxalic acid
 - . malonic acid
 - . succinic acid
 - . glutaric acid
 - . adipic acid
 - . 2,4-dimethyl adipic acid
 - . pimelic acid

- . suberic acid
- . azelaic acid
- . sebacic acid
- . dodecane dioic acid
- . fumaric acid
- . maleic acid
- cycloalkanedicarboxylic acids, such as cyclohexane 1,4-dicarboxylic acid,
- aromatic dicarboxylic acids, such as:
 - . phthalic acid
 - . isophthalic acid
 - . terephthalic acid
 - . phenylenediacetic acid
 - . naphthalene 1,5-dicarboxylic acid
 - . naphthalene 1,6-dicarboxylic acid
 - . 4,4'-diphenylcarboxylic acid
 - . 3,3'-diphenylcarboxylic acid
 - . bis(4-hydroxycarbonyl) phenyl oxide
 - . bis(3-hydroxycarbonyl) phenyl oxide
 - . 4,4'-dihydroxycarbonyl diphenylsulphone
 - . 3,3'-dihydroxycarbonyl diphenylsulphone
- pyrimidine or imidazole dicarboxylic acids.
- aminopolycarboxylic acids:
 - . ethylenediaminetetraacetic acid (E.D.T.A.)
 - . diethylenetriaminopentaacetic acid (D.T.P.A.)
 - . nitrilotriacetic acid (N.T.A.)
 - . N-(2-hydroxyethyl)ethylene diaminetriacetic acid (H.E.D.T.A.).

14 - A process according to one of claims 1 to 13, characterised in that the aqueous solution of glyoxylic acid contains monofunctional acids, in particular from 0.1 to 3% acetic acid.

15 - A process according to one of claims 1 to 14, characterised in that the aqueous solution of glyoxylic acid has a concentration which varies from 15 to 70% by weight, preferably in the region of 50% by weight.

16 - A process according to one of claims 1 to 15, characterised in that the molar ratio between the hydroxylated aromatic compound of formula (I) and the glyoxylic acid varies between 1.5 and 4.0 and is preferably selected between 2.0 and 3.0.

17 - A process according to one of claims 1 to 16, characterised in that the quantity of alkali metal hydroxide is in the region of, or equal to, the stoichiometric quantity necessary to salfify all the salifiable groups of the hydroxylated aromatic compound of formula (I) and to salfify the carboxylic function of the glyoxylic acid.

18 - A process according to one of claims 1 to 17, characterised in that the concentration of the hydroxylated aromatic compound of formula (I) is preferably comprised between 0.5 and 1.5 moles/litre, and more particularly in the region of 1 mole/litre.

19 - A process according to one of claims 1 to 18, characterised in that the quantity of catalyst used is such that the molar ratio between the catalyst and the hydroxylated aromatic compound of formula (I) is between 0.005 and 0.025, and preferably between 0.01 and 0.02.

20 - A process according to one of claims 1 to 19, characterised in that the quantity of catalyst used, as expressed by the ratio between the number of moles of catalyst and the number of moles of glyoxylic acid, is selected between 0.5 and 2.5%, preferably between 1 and 2%.

21 - A process according to one of claims 1 to 20, characterised in that the catalyst is entirely or partly provided by the aqueous solution of glyoxylic acid.

22 - A process according to claim 21, characterised in that the solution of glyoxylic acid comprises between 0.6 and 3%, preferably between 1.2 and 2.6%, by weight, of oxalic acid, as expressed in relation to the weight of glyoxylic acid.

23 - A process according to one of claims 1 to 22, characterised in that the catalyst is introduced with the aqueous solution of glyoxylic acid or into the starting reaction medium containing the hydroxylated aromatic compound of formula (I), water and the alkali metal hydroxide.

24 - A process according to one of claims 1 to 23, characterised in that the temperature of the reaction varies between 20°C and 60°C, preferably between 30°C and 40°C.

25 - Use of the optionally substituted p-hydroxymandelic compounds obtained according to one of claims 1 to 24 as intermediates for the production of hydroxyarylacetic acids, hydroxyarylglyoxylic acids, or hydroxyaromatic aldehydes.

26 - Use of p-hydroxymandelic acid and 3-methoxy p-hydroxymandelic, 3-ethoxy p-hydroxymandelic acids or 3-isopropoxy p-hydroxymandelic acids obtained in accordance with the preparation process described in one of claims 1 to 24 for the production of 4-hydroxy benzaldehyde and vanillin and analogues by oxidation of said acids.



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(54) Title: **METHOD FOR PREPARING P-HYDROXYMANDELIC COMPOUNDS OPTIONALLY SUBSTITUTED**

(54) Titre: **PROCEDE DE PREPARATION DE COMPOSES P-HYDROXYMANDELIQUES EVENTUELLEMENT SUBSTITUES**

(57) Abstract

The invention concerns a method for preparing p-hydroxymandelic compounds optionally substituted and their derivatives. More particularly, it concerns a method for preparing p-hydroxymandelic acid and methoxy-3 p-hydroxymandelic acid and their derivatives. The invention concerns a method for preparing p-hydroxymandelic compounds optionally substituted and their derivatives, which consists in condensing in water, in the presence of an alkaline agent, an aromatic compound bearing at least a hydroxyl group and whereof the position in para is free, with glyoxylic acid, said method being characterised in that the reaction is carried out in the presence of an efficient amount of a compound bearing at least two carboxylic functions.

(57) Abrégé

La présente invention a pour objet un procédé de préparation de composés p-hydroxymandéliques éventuellement substitués et dérivés. Elle vise plus particulièrement la préparation de l'acide p-hydroxymandélique et de l'acide méthoxy-3 p-hydroxymandélique et dérivés. L'invention a pour objet un procédé de préparation de composés p-hydroxymandéliques éventuellement substitués et dérivés qui consiste à effectuer la condensation dans l'eau, en présence d'un agent alcalin, d'un composé aromatique porteur d'au moins un groupe hydroxyle et dont la position en para est libre, avec l'acide glyoxylique, ledit procédé étant caractérisé par le fait que la réaction est conduite en présence d'une quantité efficace d'un composé porteur d'au moins deux fonctions carboxyliques.

**COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY
(Includes Reference to Provisional and PCT International Applications)**

Attorney's Docket No.

022701-907

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name;
I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

METHOD FOR PREPARING P-HYDROXYMANDELIC COMPOUNDS OPTIONALLY SUBSTITUTED

the specification of which (check only one item below):

- is attached hereto.
 was filed as United States application

Number _____
on _____
and was amended
on _____ (if applicable).

- was filed as PCT international application

Number PCT/FR99/01442
on 16 June 1999
and was amended
on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 (a)-(e) of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. §119:

COUNTRY (if PCT, indicate "PCT")	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 U.S.C. §119
FR	98/07586	16 June 1998	<u>X</u> Yes <u> </u> No
			<u> </u> Yes <u> </u> No
			<u> </u> Yes <u> </u> No
			<u> </u> Yes <u> </u> No
			<u> </u> Yes <u> </u> No

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below.

_____ (Application Number)

_____ (Filing Date)

_____ (Application Number)

_____ (Filing Date)

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (CONT'D)
 (Includes Reference to Provisional and PCT International Applications)

Attorney's Docket No.
 022701-907

I hereby claim the benefit under Title 35, United States Code, §120 of any United States applications(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose to the Office all information known to me to be material to the patentability as defined in Title 37, Code of Federal Regulations §1.56, which became available between the filing date of the prior application(s) and the national or PCT international filing date of this application:

PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. §120:

U.S. APPLICATIONS		STATUS (check one)		
U.S. APPLICATION NUMBER	U.S. FILING DATE	PATENTED	PENDING	ABANDONED
PCT APPLICATIONS DESIGNATING THE U.S.				
PCT APPLICATION NO.	PCT FILING DATE	U.S. APPLICATION NUMBERS ASSIGNED (if any)		

I hereby appoint the following attorneys and agent(s) to prosecute said application and to transact all business in the Patent and Trademark Office connected therewith and to file, prosecute and to transact all business in connection with international applications directed to said invention:

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (CONT'D) (Includes Reference to Provisional and PCT International Applications)		Attorney's Docket No. 022701-907
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